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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/635,108	SCARINGE, STEPHEN	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/08/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Workgroup 1630, Art Unit 1634, and has been docketed to Primary Examiner Bradley L. Sisson.

Specification

2. The specification is objected to as documents have been improperly incorporated by reference. Attention is directed to pages 8 and 12 of the disclosure where documents have been incorporated by reference but the specification does not identify with detailed particularity what specific information it incorporates nor does the specification clearly indicate where that material is to be found in he various documents. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific

reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

5. For convenience, claims 1, 9, and 10, the only independent claims, are reproduced below.

1. An interfering hairpin RNA having the structure X_1-L-X_2, wherein X_1 and X_2 are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a loop region comprising a non-nucleotide linker molecule, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of said target RNA.

9. A method for inhibiting a mRNA, comprising:

a) providing an interfering hairpin RNA having the structure X_1-L-X_2, wherein X_1 and X_2 are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a loop region comprising a non-nucleotide linker molecule, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of said target RNA; and

b) contacting shRNA with a sample containing or suspected of containing the mRNA under conditions that favor intermolecular hybridization between the shRNA and the target mRNA whereby presence of the shRNA the target mRNA.

A method for assaying whether a gene product is a suitable target for drug discovery comprising:

a) introducing an shRNA which targets the mRNA of the gene for degradation into a cell or organism, wherein said shRNA having the structure X_1-L-X_2, wherein X_1 and X_2 are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a loop region comprising a non-nucleotide linker molecule, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of said double-stranded RNA;

b) maintaining the cell or organism of (a) under conditions in which degradation of the mRNA occurs, resulting in decreased expression of the gene; and

c) determining the effect of the decreased expression of the gene on the cell or organism, wherein if decreased expression has an effect, then the gene product is a target for drug discovery.

6. For purposes of examination, claim 1 has been interpreted as encompassing virtually any RNA sequence, including, but not limited to those that possess any biological activity" (page 3, line 26), or can be used in the treatment of any "plant, animal or human suspected of having or being prone to a disease or condition associated with expression of a target gene" (page 4 second

paragraph, of the specification). Said RNA and method of inhibiting mRNA (claim 9) have also been interpreted as fairly encompassing the "knocking down (partially or completely) a targeted gene, for example for generating models of disease states, to examine the function of a gene, to assess whether an agent acts on a gene, to validate targets for drug discovery, etc." (specification at page 10, fist paragraph). Said RNA has also been interpreted as encompassing shRNAs that are to be utilized "for diagnostics, therapeutics, prophylaxis and as research reagents and kits" (specification at page 10, third paragraph).

7. A review of the disclosure finds but two examples.

Example 1, "Hairpin design," pages 11-14; and

Example 2, "Hairpin design with different overhangs," pages 14-15.

8. A review of the disclosure fails to find an adequate written description of the virtually infinite number of possible "interfering hairpin NRA" and "short interfering RNA." While the examples make reference to the synthesis of hairpins designed with 6 different core sequences, a review of the specification fails to provide an adequate written description of these sequences such that one of skill in he art would be able to recognize then, or any other claimed molecule over that not encompassed by the claims.

Rather than provide an adequate description of the innumerable short interfering hairpin RNA sequences claimed, applicant are seemingly relying upon obviousness to satisfy the written description requirement. Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

While page 12, last paragraph, of the specification directs attention to US Patent 6,111,086 as to protocols that are to relied upon in synthesizing the oligonucleotides, and seeks to incorporate said document by reference, the '086 patent, as noted above, has not been properly incorporated by reference and therefore cannot now be relied upon for satisfaction of either the written description, enablement or best mode requirements under 35 USC 112, first paragraph. Therefore, and in the absence of convincing evidence to the contrary, claims 1-10 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re*

> *Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

9. As presented above, the specification teaches that the short interfering hairpin RNA is to be used in a variety of methods, including used in the treatment of any "plant, animal or human suspected of having or being prone to a disease or condition associated with expression of a target gene" (page 4 second paragraph, of the specification). Said RNA and method of inhibiting mRNA (claim 9) have also been interpreted as fairly encompassing the "knocking down (partially or completely) a targeted gene, for example for generating models of disease states, to examine the function of a gene, to assess whether an agent acts on a gene, to validate targets for drug discovery, etc." (specification at page 10, fist paragraph). Said RNA has also been interpreted as encompassing shRNAs that are to be utilized "for diagnostics, therapeutics, prophylaxis and as research reagents and kits" (specification at page 10, third paragraph).
A review of the disclosure fails to find where any one, much less all of the intended utilities have been fully enabled by the specification. Further, the specification fails to set forth the requisite starting materials and reaction conditions that would permit one of skill in the art at the time the invention was made to reproducibly manufacture any and all useful interfering hairpin RNA molecules. While the specification makes reference to various documents, said documents have not been properly incorporated by reference and therefore cannot be used or otherwise relied

upon for satisfaction of the enablement requirements of 35 USC 112, first paragraph. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. <u>However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.</u> It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

10. With no specific starting material or reaction conditions provided, the skilled artisan would have to resort to trial and error experimentation with little if any reasonable expectation of success. Such level of effort required to the exerted by the skilled artisan is undue. Therefore, and in the absence of convincing evidence to the contrary, claims 1-10 are rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. The term "short" in claims5-8 is a relative term, which renders the claims indefinite. The term "short" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

Claims 1-10 are indefinite with respect to what constitutes the metes and bounds of "interfering." Claim 10 lacks antecedent support for "the mRNA", "the gene," and "said double-stranded RNA."

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dervan in view of Yu et al.

17. Dervan teaches the production of hairpin nucleic acids that have an X_1-L-X_2 conformation where X_1 and X_2 are two nucleotide sequences that are at lest partially complementary and where L is a non-nucleotide linker.

18. The molecule can be optionally labeled and used in a variety of methods, including diagnostics, cytohistology, and radiotherapy (column 7). Also disclosed at column 7 are a plethora of suitable labels. Columns 11-14 disclose additional methods in which they can be used, including inhibition of transcription (column 13).

19. Column 10 teaches various permutations to forming the hairpin molecule.

20. Dervan do not teach that the complementary nucleic acids are RNA.

21. Yu et al., disclose RNA interference by expression of short-interfering RNA and hairpins. At page 6047, right column, last paragraph, Yu et al., teach producing short interfering RNA (siRNA) oligonucleotides based on DNA oligonucleotides.

22. Yu et al., page 6049, right column teach inhibition of RNAs complementary to either the sense or antisense RNA. Such inhibition teaches a limitation of claim 9, drawn to a method of inhibiting mRNA. Page 6052 teaches the use of short interfering RNA in identifying gene function and for gene therapy. Such disclosures meet a limitation of claim 10, drawn to a method of assaying whether a gene product is a suitable target for drug discovery.

23. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the procedure of Dervan with that of Yu t al., such that the X_1-L-X_2 conformation and it benefits was applied to a short interfering hairpin RNA. As presented above, short interfering hairpin RNA had been developed and had been found quite useful in identifying genes and would be useful in gene therapy. By adapting the X_1-L-X_2 conformation, the skilled artisan would be able to take advantage of the reduced steric hindrance found in a normal hairpin as afforded by the flexibility of the linker. In view of such detailed teachings, the reproducibility, and the wide application, the ordinary artisan would have been both well motivated and would have had a most reasonable expectation of success.

24. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-10 are rejected under 35 USC 103(a) as being unpatentable over Dervan in view of Yu et al.

Conclusion

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

26. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

27. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
March 22, 2004